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(54) **Novel basic derivatives of benz(e)isoindol-1-ones and pyrrolo(3,4-c)quinolin-1-ones with 5-HT3-antagonistic activity, their preparation and their therapeutic use**

Neue basische Derivate von Benz(e)isoindol-1-onen und Pyrrolo(3,4-c)chinolin-1-onen mit 5-HT3-antagonistischer Aktivität, ihre Herstellung und ihre therapeutische Verwendung

Nouveaux dérivés basiques des benz(e)isoindol-1-ones et pyrrolo(3,4-c)quinolin-1-ones ayant une activité antagoniste 5-HT3, leur préparation et leur utilisation thérapeutique

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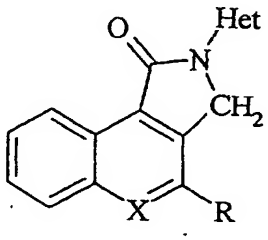
Description

[0001] The subject of the present invention novel basic derivatives of benz[e]isoindol-1-ones and pyrrolo[3,4-c]quinolin-1-ones which can be represented by the general formula (I) indicated below:



(I)

and in which

- X is CH or N,
- R is H, Cl or OR_1 in which R_1 is H or an alkyl group having from 1 to 3 carbon atoms,
- Het is the 3-endotropyl group (that is, the 8-methyl-8-azadicyclo[3.2.1]oct-3-yl group) or the 3-quinuclidyl group (that is, the 1-azadicyclo[2.2.2]oct-3-yl group).

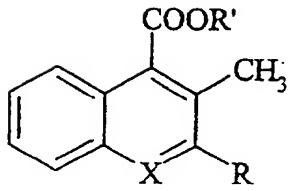
[0002] The compounds of the present invention have been found to be potent and selective antagonists of the 5-HT_3 serotoninergic receptor and can therefore advantageously be used in the treatment of various diseases in man, for example, as anti-emetics, particularly for vomiting associated with antitumoral chemotherapy, and in various pathological conditions of the central nervous system such as, for example, anxiety, depression, schizophrenia, psychosis, Alzheimer's disease and senile dementia, and also as antitussives. Since serotonin is also known to be involved in the regulation of the peristalsis of the gastrointestinal tract, the compounds of the invention can also advantageously be used as prokinetic agents in various pathological conditions connected with hypomotility of the gastrointestinal tract such as, for example, non-ulcerous dyspepsia, reflux oesophagitis and in irritable bowel syndrome.

[0003] In addition to the compounds currently used in treatment as anti-emetics, such as Granisetron and Ondasetron, many publications and patents describe novel compounds with 5-HT^3 antagonistic activity. Thus, for example, US patent 5200413 describes N-azadicyclo-indol-1-carboxyamides with 5-HT-antagonistic activity; US patent 5260303 describes azacyclo-imidazopyridines with 5-HT_3-antagonistic activity, US patent 5280028 describes benzimidazole derivatives active as 5-HT_3-antagonists and 5-HT_4-antagonists, US patent 5399562 describes indolone derivatives substituted with groups such as endotropyl and quinuclidyl groups. Recently, tropylazaindole derivatives with mixed 5-HT_3- and sigma-oppioidantagonist activity having antitussive activity (WO 04742-A-1995), 1-heteroaryl-4-alkyl-4-aminopiperidine derivatives which easily overcome the blood-brain barrier [EP-647639-A (1995)], tetrahydrobenzimidazole derivatives with mixed anti-5-HT_3 and H_3 histamine activity [WO 9509168-A(1995)] and imidazol-4-yl-piperidine derivatives with mixed anti-5-HT_3 and -5-HT_4 activity (EP-646583-A(1995)] have also been described. All of this research shows that there is a great therapeutic need to find novel, ever more potent, selective and better tolerated drugs with 5-HT_3-antagonistic activity. In accordance with this need, the object of the present invention is to provide novel drug treatments having potent and selective -5-HT_3-antagonistic activity for the treatment of all pathological conditions, both central and peripheral, which are due to poor operation of the -5-HT_3 serotoninergic receptor system. Pharmaceutical forms of the compounds of the invention can be prepared by conventional techniques, for example, as tablets, capsules, suspensions, solutions, suppositories or patches, and may be administered orally, parenterally, rectally or transdermally, or as other forms suitable for achieving the therapeutic effect such as, for example, solid preparations for oral use with protracted action which permit controlled release of the active substance over time.

[0004] The active ingredient is normally administered to the patient with a reference dose variable from 0.001 to 1 mg/kg of body weight per dose. For parenteral administration, the use of a water-soluble salt of the compounds of the invention, such as the hydrochloride or another non-toxic and pharmaceutically acceptable salt, is preferable. As inactive ingredients, substances commonly used in pharmaceutical technology such as excipients, binders, flavourings, disaggregants, colourings, humectants, etc. may be used.

[0005] The method of preparing the derivatives of the invention consists of a series of reactions which comprise:

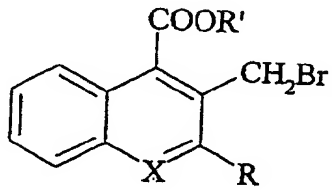
a) reacting esters of formula (IV)



(IV)

prepared as described by Mayer et al (Berichte 1922, 55, 1835-1861), in which X and R have the meanings given above and R' may be methyl or ethyl, with N-bromosuccinimide in the presence of benzoyl peroxide, in an organic solvent such as, for example, carbon tetrachloride, at a temperature between ambient temperature and the reflux temperature of the solvent, for a period of between 1 and 8 h, to give the corresponding 2-bromomethyl derivatives of formula III (see Synthesis scheme 1, step 1);

b) reacting the bromo derivatives of formula III



(III)

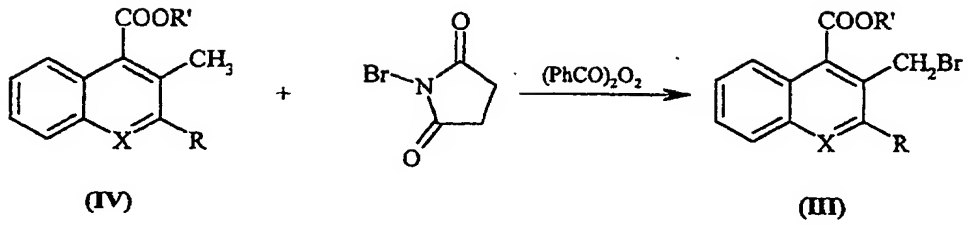
with a stoichiometric quantity of a heterocyclic amine of formula (II)

NH_2-Het (II)

in which Het is the 3-endotropyl group, that is, the 8-methyl-8-azadicyclo[3.2.1]oct-3-yl group, in the presence of an inert tertiary base which functions as a proton acceptor, or with an excess of the amine (II), at the reflux temperature of an anhydrous solvent, preferably toluene, for a period of between 1 and 24 h, to give the corresponding amide derivatives of formula (I) in accordance with Synthesis scheme 1, step 2. The compounds of formula (I) in which R is OH are prepared by hot acid hydrolysis of the corresponding ethereal derivatives.

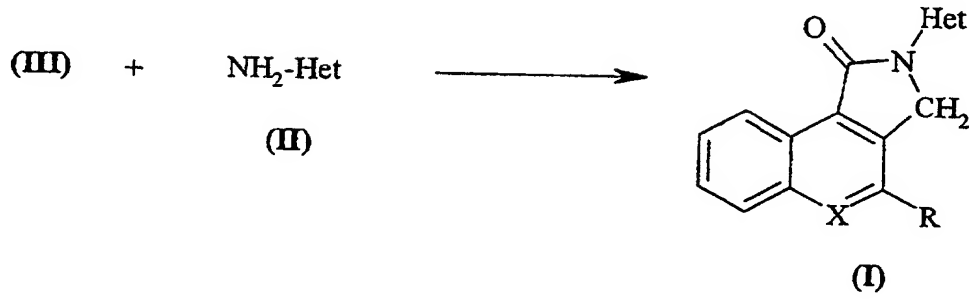
Synthesis scheme 1

Step 1



Step 2

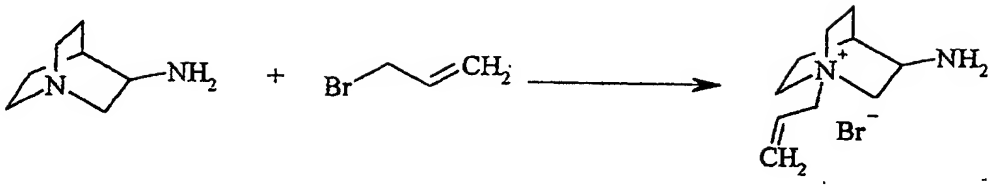
in which Het is the 3-endotropyl (8-CH_3-8-azadicyclo[3.2.1] oct-3-yl) group



[0006] The method for the preparation of the derivatives of the invention in which Het is the 3-quinuclidyl group (that is, the 1-azadicyclo[2.2.2]oct-3-yl group) consists of a series of reactions illustrated by Synthesis scheme 2, comprising: protecting the tertiary endocyclic nitrogen of the 3-aminoquinuclidine by alkylation with allyl bromide, reacting the non-isolated quaternized intermediate (VI) with the appropriate bromine derivative of formula (III) indicated in Scheme 1, to give the quaternary ammoniacal salt of the cyclized compound (V) which, in turn, is not isolated, and deprotecting hot with n-dipropylamine in dimethyl formamide in the presence of a catalytic quantity of $Pd(PPh_3)_2Cl_2$ to give amide derivatives of formula (I) according to Synthesis scheme 2, step 3, in which Het is the 3-quinuclidyl group and X and R have the meanings given above.

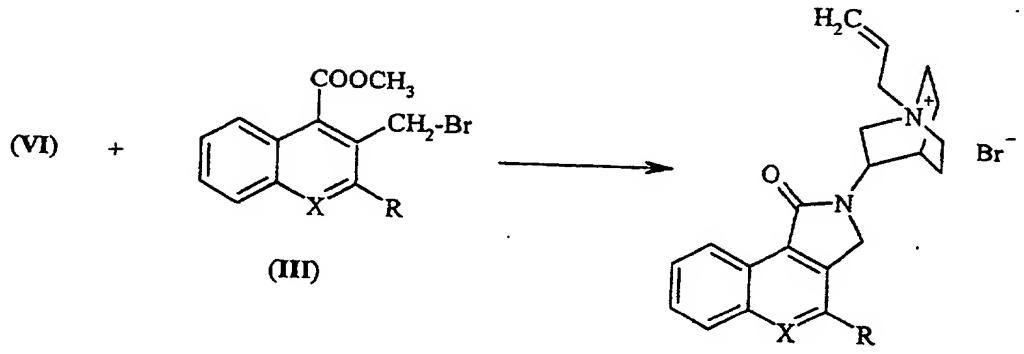
Synthesis scheme 2

Step 1



3-NH_2-quinuclidine Allyl bromide (VI) (non-isolated)

Step 2

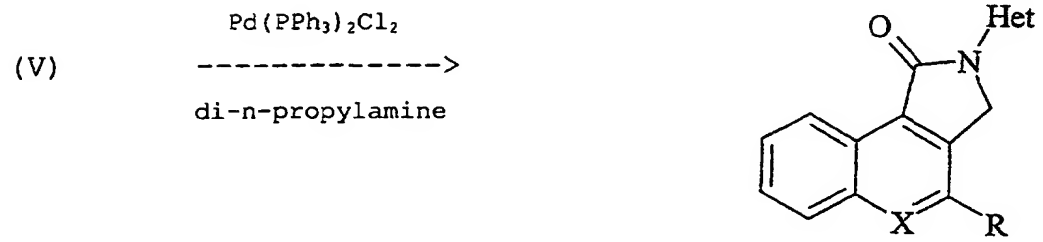


(III)

(V)

(non-isolated)

Step 3



(I)

in which Het is the 3-quinuclidyl group (that is, the 1-azadicyclo[2.2.2.]oct-3-yl group).

[0007] The following examples are given below to illustrate the invention further.

Example 1

***endo*-2-[8-methyl-8-azadicyclo[3.2.1.]oct-3-yl-2,3-dihydro-1*H*-benz[e]isoindol-1-one (Compound 1 of Table 1)**

[0008] A mixture constituted by 10 g (51 mmoles) of 2-methyl-1-naphthalene methyl carboxylate, 9.9 g (55.6 mmoles) of N-bromosuccinimide, and 1.5 g (6.2 mmoles) of benzoyl peroxide in 300 ml of CCl_4 was heated under reflux for 2 h. The solvent was evaporated, the residue was taken up with the minimum quantity of CCl_4, the succinimide was filtered out, and the filtrate was evaporated under reduced pressure to give 15 g of yellowish oil which was used as such for the subsequent reaction (NMR indicated that this oil was constituted by 85-95% of 2-bromomethyl-1-naphthalene methyl carboxylate). A mixture of 15 g of this oil with 25.9 g (185 mmoles) of *endo*-3-aminotropane in 500 ml of toluene was heated under reflux for 8 h with azeotropic removal of the methanol evolved in the course of the reaction. The solvent was evaporated under reduced pressure, the residue was taken up with $CHCl_3$, washed with water and then with a saturated NaCl solution, dehydrated and evaporated under reduced pressure. The oily residue, treated with hexane-ethyl acetate, was rendered friable by resting. It was recrystallized from ethyl acetate, to give 8.5 g. Yield 54.5%. Melting point 174-175°C. ^{1}H NMR ($CDCl_3$): 1.54-1.61 (m, 4H), 2.15-2.19 (m, 2H), 2.25-2.60 (m, 5H), 3,28 (m, 2H), 4.41 (s, 2H), 4.64 (m, 1H), 7.47-7.67 (m, 3H), 7.90 (d, J=7.6, 1H), 7.97 (d, J=8.3, 1H), 9.24 (d, J=8.4, 1H).

Example 2

***endo*-2-[8-methyl-8-azadicyclo[3.2.1]oct-3-yl]-2,3-dihydro-1*H*-pyrrolo[3,4-c]quinolin-1-one (Compound 2 of Table 1)**

[0009] The method described in Example 1 was followed with the use of 3-methyl-4-quinoline ethyl carboxylate instead of the 2-methyl-1-naphthalene methyl carboxylate. After reaction with N-bromosuccinimide and in the presence of benzoyl peroxide, the corresponding 3-bromomethyl-4-quinoline ethyl carboxylate, a dense yellow-orange oil, was obtained and was reacted with an excess of endo-3-aminotropane in toluene under reflux for 8 h. Upon completion the oily residue obtained was rendered friable and crystallized from an n-hexane-ethyl acetate mixture. Overall yield 38%. Melting point 153-154°C. ^{1}H NMR ($CDCl_3$): 1.50-1.65 (m, 4H), 2.14-2.21 (m, 5H), 2.42-2.59 (m, 2H), 3,28 (m, 2H), 4.46 (s, 2H), 4.61 (m, 1H), 7.61-7.79 (m, 2H), 8.15 (d, J=8.4, 1H), 9.05 (m, 2H), MS: m/z 307 (M^+, 22).

Example 3

***endo*-2-[8-methyl-8-azadicyclo[3.2.1]oct-3-yl]-2,3-dihydro-4-chloro-1*H*-pyrrolo[3,4-c]quinolin-1-one (Compound 3 of Table** 1)

[0010] This compound was synthesized by following the method used for the synthesis of Compound 1, with the use of 8.7 g (35 mmoles) of 2-chloro-3-methyl-4-quinoline ethyl carboxylate instead of the 2-methyl-1-naphthalene methyl carboxylate and in accordance with the stoichiometry described above. 7.2 g of Compound 3 was obtained (yield 60%). Recrystallization from *n*-hexane-ethyl acetate gave a pure product which melted at 169-171°C. ^{1}H NMR ($CDCl_3$): 1.47-1.66 (m, 4H), 2.16-2.23 (m, 5H), 2.45-2.60 (m, 2H), 3.29 (m, 2H), 4.41 (s, 2H), 4.67 (m, 1H), 7.64-7.83 (m, 2H), 8.09 (d, J=8.3, 1H), 9.04 (d, J=8.6, 1H), MS: m/z 341 (M^+, 16).

Example 4

***endo*-2-[8-methyl-8-azadicyclo[3.2.1]oct-3-yl]-2 ,3-dihydro-4-propoxy-1*H*-pyrrolo[3,4-c]quinolin-1-one (Compound 4 of Table** 1)

[0011] This compound was synthesized by following the method used for the synthesis of Compound 1, with the use of 2.6 g (9.5 mmoles) of 2-propoxy-3-methyl-4-quinoline ethyl carboxylate instead of the 2-methyl-2-naphthalene methyl carboxylate and in accordance with the stoichiometry described above. 1.5 g of Compound 4 was obtained (yield 43%). After crystallization from *n*-hexane-ethyl acetate, a pure compound in the form of colourless needles which melted at 170-171°C was obtained. ^{1}H NMR ($CDCl_3$): 1.08 (t, J=7.4, 3H), 1.48-1.67 (m, 4H), 1.80-1.98 (m, 2H), 2.19-2.23 (m, 5H), 2.43-2,58 (m, 2H), 3.28 (m, 2H), 4.33 (s, 2H), 4.50-4.73 (m, 3H), 7.48 (t, J=7.4, 1H), 7.65 (t, J=8.1, 1H), 7.90 (d, J=8.3, 1H), 8.93 (d, J=9.0, 1H).

Example 5

***endo*-2-[8-methyl-8-azadicyclo[3.2.1]oct-3-yl]-2,3-dihydro-4-hydroxy-1*H*-pyrrolo[3,4-c]quinolin-1-one (Compound 5 of Table 1)**

[0012] 8 g (24.9 mmoles) of Compound 3 was dissolved in 1 litre of 1N HCl and heated to 80°C for 4 h with stirring. The reaction mixture was then cooled to 0°C, brought to pH 9 with 5N NaOH and extracted with chloroform. The organic extracts were dehydrated with anhydrous sodium sulphate, filtered and evaporated at reduced pressure to give 7 g of Compound 5 (yield 88%). Crystallization from ethyl acetate, gave a pure compound which melted at 245-246°C. ^{1}H NMR ($CDCl_3$): 1.46-1.61 (m, 4H), 2.16-2.23 (m, 5H), 2.43-2.58 (m, 2H), 3.27 (m, 2H), 4.35 (s, 2H), 4.61 (m, 1H), 7.28-7.36 (m, 2H), 7.55 (m, 1H), 8.84 (d, j=8.2, 1H), 10.63 (br s, 1H), MS: m/z 323 (M^+, 28).

Example 6

(R,S)-2-[1-azadicyclo [2.2.2]oct-3-yl]-2,3-dihydro-1*H*-benz[*e*]isoindol-1-one (Compound 6 of Table 1)

[0013] A suspension of 11.2 g (56 mmoles) of 3-aminoquinuclidine dihydrochloride, 22 g (207 mmoles) of anhydrous Na_2CO_3, and - 300 ml of ethanol was heated under reflux in an inert atmosphere with vigorous stirring for 1 h and was then cooled to ambient temperature and supplemented with 4.8 ml (55 mmoles) of allyl bromide. The mixture was allowed to react with stirring at ambient temperature for 20 min. and then heated under reflux for 1 h and finally supplemented with 14.6 g (50 mmoles) of 2-bromomethyl-1- naphthalene methyl carboxylate (prepared as described in the synthesis method of Example 1) dissolved in the minimum quantity of ethanol. The resulting mixture was heated under reflux for 12 h. The solvent was evaporated under reduced pressure and the residue was taken up with 500 ml of dimethyl formamide. The solid which had not dissolved was filtered out and the filtrate was supplemented with 40 ml (292 mmoles) of dipropylamine and 0.5 g (0.71 mmoles) of $Pd(PPh_3)_2Cl_2$. The resulting mixture was heated to 100°C for about 30 minutes in an inert nitrogen atmosphere and then poured into water and ice and extracted with $CHCl_3$. The extracts were washed thoroughly with water, dehydrated over sodium sulphate and evaporated at reduced pressure. The semi-solid residue which was obtained was solidified as a result of repeated washings with ethyl ether. 5.1 g of pure, solid, microcrystalline Compound 6 was thus obtained. Yield 34%. Melting point 138-141°C. ^{1}H NMR ($CDCl_3$): 1.59-1.96 (m, 4H), 2.20 (m, 1H), 2.89-3.18 (m, 5H), 3.41 (m,1H), 4.48 (t, J=8.3, 1H), 4.64 (m, 2H), 7.49-7.68 (m, 3H), 7.90 (d, J=8.1, 1H), 7.98 (d, J=8.4, 1H), 9.20 (d, J=8.3, 1H).

Example 7

(S)-2-[1-azadicyclo[2.2.2]oct-3-yl]-2,3-dihydro-1*H*-benz[*e*]isoindol-1-one (Compound 7 of Table 1)

[0014] The (S) enantiomer of Compound 6 was prepared by following the method described above for Compound 6, with the use of (S)-3-aminoquinuclidine dihydrochloride instead of (R, S) -3-aminoquinuclidine dihydrochloride. Yield 32%. Melting point 152-154°C.

Example 8

(R)-2-[1-azadicyclo[2.2.2]oct-3-yl]-2,3-dihydro-1*H*-benz[*e*]isoindol-1-one (Compound 8 of Table 1)

[0015] The (R) enantiomer of Compound 6 was prepared by following the method described above for Compound 6, with the use of (R)-3-aminoquinuclidine dihydrochloride instead of (R, S) -3-aminoquinuclidine dihydrochloride. Yield 35%. Melting point 155-157°C.

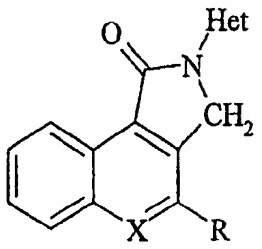
Example 9

(R,S)-2-[1-azadicyclo[2.2.2]oct-3-yl]-2,3-dihydro-1*H*-pyrrolo[3,4-c]quinolin-1-one (Compound 9 of Table 1)

[0016] The method described for the preparation of Compound 6 was followed, with the use of 3-bromomethyl-4-quinoline ethyl carboxylate instead of 2-bromomethyl-1-naphthalene methyl carboxylate. Upon completion, the oily residue obtained was rendered friable with n-hexane to give an amorphous solid without a definite melting point. Calculated analysis for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.98, H, 6.66, N, 13.99.

[0017] Some derivatives of formula (I) produced in accordance with the invention are given in Table 1 below with some identifying chemical and physical characteristics, without thereby in any way limiting the spirit and subject of the invention.

Table 1: Compounds of formula (I)



Compounds	X	Het	R	Formula	Melting point	Crystallization solvents
1	CH	3-endo-tropyl[1]	H	$C_{20}H_{22}N_2O$	174-175°C	ethyl acetate
2	N	3-endo-tropyl	H	$C_{19}H_{21}N_3O$	153-154°C	n-hexane-ethyl acetate
3	N	3-endo-tropyl	Cl	$C_{19}H_{20}ClN_3O$	169-171°C	n-hexane-ethyl acetate
4	N	3-endo-tropyl	OC_3H_7	$C_{22}H_{27}N_3O_2$	170-171°C	n-hexane-ethyl acetate
5	N	3-endo-tropyl	OH	$C_{19}H_{21}N_3O_2$	245-246°C	ethyl acetate
6(R,S)	CH	3-quinuclidyl[2]	H	$C_{19}H_{20}N_2O$	153-154°C	n-hexane-ethyl ether
7(S)	CH	3-quinuclidyl	H	$C_{19}H_{20}N_2O$	152-154°C	n-hexane-ethyl ether
8(R)	CH	3-quinuclidyl	H	$C_{19}H_{20}N_2O$	155-157°C	n-hexane-ethyl ether
9	N	3-quinuclidyl	H	$C_{18}H_{19}N_3O$	amorphous	-

(1): 3-tropyl = 8-methyl-8-azadicyclo[3.2.1.]oct-3-yl

(2): 3-quinuclidyl = 1-azadicyclo[2.2.2]oct-3-yl

DESCRIPTION OF PHARMACOLOGICAL ACTIVITY

[0018] In order to evaluate the affinity of the compounds of the invention for the various subtypes of serotoninergic receptors, [3H]-BRL43694 (Granisetron) was used as a marked ligand for the investigation of the 5-HT_3 receptors, [3H]-paroxetine was used for the investigation of the serotonin uptake site, [3H]-ketanserine was used for the investigation of the 5-HT_2 receptors and [3H]-8-OH DPAT was used for the investigation of the 5HT-1A receptors.

a) Affinity for the 5-HT_3 receptors

[0019] The method of Nelson et al. (Biochem. Pharmacol. 1989, 38, 1693-95) was followed with slight modifications. Rat cortex and hippocampus were used to produce a pellet having a final concentration of 20 mg of tissue/sample. Specific activity of the tracer: 81 Ci/mmole; incubation time: 30 min; incubation temperature: 25°C. Specific binding: 70% of the total; Kd = 0.6 x 10^{-9}M.

b) Affinity for the serotonin uptake site

[0020] The method of Plenge et al (Eur. J. Pharmacol., 1990, 189, 129-134) was followed with slight modifications. The entire rat brain was used to produce a pellet having a final concentration of 2 mg of tissue/sample. Specific activity of the tracer: 29.7 Ci/mmole; incubation time: 60 min.; incubation temperature: 25°C. Specific binding: 75% of the total; Kd = 0.09 x 10^{-9}M.

c) Affinity for the 5-HT_2 receptors

[0021] The method of Leysen et al (Mol. Pharmacol. 1982, 21 , 301-314) was followed with slight modifications. Rat prefrontal cortex was used to produce a pellet having a final concentration of 8 mg of tisssue/sample. Specific activity of the tracer: 80.9 Ci/mmole; incubation time: 20 min; incubation temperature: 37°C. Specific binding: 90% of the total; Kd = 0.5 x 10^{-9}M.

d) Affinity for the 5-HT_{1A} receptors

[0022] The method of Hall et al (J. Neurochem. 1985, 44, 1685-1696) was followed with slight modifications. Rat hippocampus was used to produce a pellet having a final concentration of 4 mg of tissue/sample. Specific activity of the tracer: 137 Ci/mmole; incubation time 10 min; incubation temperature: 37°C. Specific binding: 80% of the total; Kd = 2.3 x 10^{-9}M.

[0023] It can be seen from the data given in Table 2 that many of the compounds of the invention are potent antagonists of the 5-HT_3 subtype receptor. For example Compound 7 has a sub-nanomolar affinity for the 5-HT_3 receptor and was the most active of all of the compounds tested. The compounds of the invention were also shown to possess a high selectivity for this receptor since they were very slightly active or inactive at the other receptor subtypes tested. It is also interesting to note that even small structural variations of the compounds of the invention cause a significant loss of affinity for the 5HT_3 receptor. Thus, for example, Compound 10, that is, the analogous 3-hexotropyl derivative of the corresponding 3-endotropyl (Compound 1), described herein purely for comparative purposes, was almost 2 orders of logarithmic magnitude less active than Compound 1; similarly, Compound 11 which is also given for comparative purposes, that is *endo*-2-[8-methyl-8-azadicyclo[3.2.1]oct-3-yl]-2,3-dihydro-1H-pyrrolo[3,4-*b*]quinolin-1-one, which has a "linear" polycyclic fusion and which is the pyrrolo-quinoline analogue of Compound 2 was approximately 60 times less active than the latter, in which the polycyclic fusion takes place on the "e" face and is hence angular.

Activity in vivo

[0024] The potent 5-HT_3-antagonistic activity performed by the compounds of the invention in vitro was confirmed in vivo in the rat in the bradycardial reflex test according to Bezold-Jarisch (Paintal, Physio. Rev. 1973, 53, 159). Serotonin injected i.v. induced a bradycardial effect in the rat. Products 1-9 of the invention, injected in doses of 0.1 mg/kg i.v. 5 minutes before the administration i.v. of 0.03 mg/kg of serotonin completely blocked the bradycardial effect induced thereby. It should be noted that the same compounds injected alone, even in doses 10 times higher, did not induce any variation in cardiac frequency in the rat, thus behaving as pure antagonists.

Table 2: Affinity of some compounds of the invention for binding to various serotonin receptor subtypes (Ki (nM) ± SE)

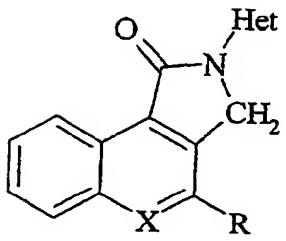
Compound	5-HT_3 Subtype ([3H]-BRL43694)	5-HT Uptake ([3H]-paroxetin)	5-HT_{2A} Subtype ([3H]-ketanserine)	5-HT_{1A} Subtype ([3H]-8OH-DPAT)
1	1.0 ± 0.2	632 ± 51	21110 ± 2300	30619 ± 6460
2	1.3 ± 0.2	503 ± 86	IN (10^{-6}M)	IN (10^{-6}M)
3	2.6 ± 0.4	175 ± 30	IN (10^{-6}M)	IN (10^{-6}M)
4	0.7 ± 0.2	108 ± 15	IN (10^{-6}M)	IN (10^{-6}M)
5	0.9 ± 0.06	485 ± 37	IN (10^{-6}M)	IN (10^{-6}M)
6	0.7 ± 0.08	95.8 ± 9.6	26477 ± 8700	IN (10^{-6}M)
7	0.3 ± 0.09	-	-	-
8	1.8 ± 0.5	-	-	-
9	1.6 ± 0.6	123.7 ± 22	IN (10^{-6}M)	IN (10^{-6}M)
10*	85.5 ± 16	-	-	-
11**	87 ± 37	-	-	-
serotonin	118 ± 34	738 ± 117	-	7.3 1.3
quipazine	1.8 ± 0.3	31.3 ± 2.9	1808 ± 476	3649 ± 799
Granisetron	0.6 ± 0.06	-	-	-
6-NO_2-quipazine	-	0.12 ± 0.01	-	-
8-OH-DPAT	-	-	-	1.18 ± 0.13

(*): 3-hexotropyl analogue of Compound 1

(**): compound given for comparative purposes (see test)

Claims

1. Compounds which can be represented by the general formula (I) indicated below:



(I)

and in which:

- X is CH or N;
- R is H, Cl or OR_1 in which R_1 is H or an alkyl group having from 1 to 3 carbon atoms,
- Het is the 3-endotropyl group (that is, the 8-methyl-8-azadicyclo[3.2.1]oct-3-yl group) or the 3-quinuclidyl group [that is, the 1-azadicyclo[2.2.2]oct-3-yl group], and their salts produced from pharmaceutically acceptable inorganic or organic acids.

2. Compounds according to Claim 1 in which X is CH.

3. Compounds according to Claim 1 in which X is N.

4. Compounds according to Claim 2 in which Het is the 3-endotropyl group.

5. Compounds according to Claim 2 in which Het is the 3-quinuclidyl group.

6. Compounds according to Claim 3 in which Het is the 3-endotropyl group.

7. Compounds according to Claim 3 in which Het is the 3-quinuclidyl group.

8. A pharmaceutical preparation comprising, as an active substance, at least one of the compounds according to Claim 1 or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical preparation according to Claim 8 for therapeutic use in accordance with its activity in the treatment of spontaneous or post-operative nausea and vomiting or nausea or vomiting induced by cytostatic therapy.

10. A pharmaceutical preparation according to Claim 8 for the treatment of pathological conditions of the CNS connected with imbalances in the physiological neurone levels of serotonin, such as, for example, anxiety, panic attacks, psychosis, depression, Alzheimer's disease, etc., or with other causes correlated with the mechanism of action of the compounds according to Claim 1.

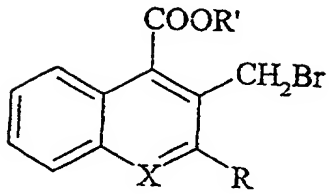
11. A pharmaceutical preparation according to Claim 8 for use in the treatment of disorders of the gastrointestinal system such as non-ulcerous dyspepsia, oesophagitis due to reflux, irritable colon and motility disturbances.

12. A pharmaceutical preparation according to Claim 8 for the symptomatic treatment of coughs.

13. A pharmaceutical preparation according to Claim 8, further comprising pharmaceutically acceptable inactive ingredients selected from the group which consists of vehicles, binders, flavourings, disaggregants, preservatives, humectants, and mixtures thereof, or ingredients which facilitate transdermal absorption or which permit controlled release of the active substance over time.

14. A method for the preparation of a derivative of general formula (I) in which X and R have the meanings given in Claim 1, and Het is the 3-endotropyl group, that is, the 8-methyl-8-azadicyclo[3.2.1]oct-3-yl group, comprising the steps of:

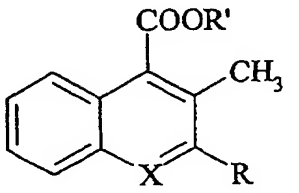
a) reacting esters of formula (IV)



(IV)

in which X and R have the meanings given above and R' may be methyl or ethyl with N-bromosuccinimide in the presence of benzoyl peroxide in an organic solvent such as, for example, carbon tetrachloride, at a temperature between ambient temperature and the reflux temperature of the solvent, for a period of between 1 and 8 h, to give the corresponding 2-bromomethyl derivatives of formula III;

b) reacting the bromo-derivatives of formula III



(III)

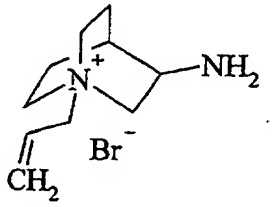
with a stoichiometric quantity of a heterocyclic amine of formula (II)

$$NH_2\text{-Het} \qquad \text{(II)}$$

in which Het is the 3-endotropyl group, in the presence of an inert tertiary base which functions as a proton acceptor, or with an excess of the amine (II), at the reflux temperature of an anhydrous solvent, preferably toluene, for a period of between 1 and 24 h, to give the corresponding amide derivatives of formula (I), which are isolated as such or in the form of pharmaceutically acceptable salts, the compounds of formula (I) in which R is OH being prepared by hot acid hydrolysis of the corresponding ethereal derivatives.

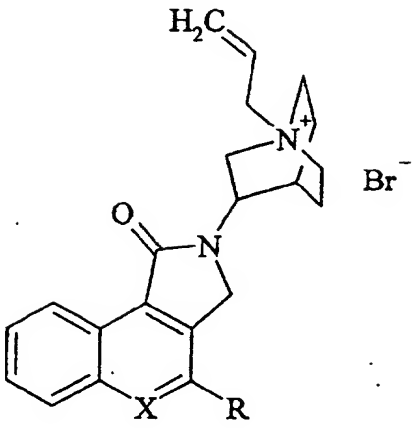
15. A method for the preparation of a derivative of general formula (I) in which X and R have the meanings given in Claim 1 and Het is the 3-quinuclidyl group, that is, the 1-azadicyclo[2.2.2]oct-3-yl group, comprising the steps of:

protecting the tertiary endocyclic nitrogen of the 3-aminoquinuclidine by alkylation with allyl bromide, reacting the non-isolated quaternized intermediate (VI)



(VI)

with the appropriate bromine derivative of formula (III) indicated in Claim 14, to give the quaternary ammoniacal salt of cyclized compound (V),

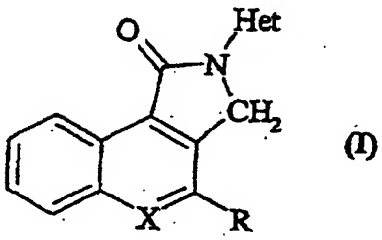


(V)

which, in turn, is non isolated, and deprotecting hot with n-dipropylamine in dimethyl formamide and in the presence of a catalytic quantity of $Pd(PPh_3)_2Cl_2$ to give the corresponding amide derivatives of formula (I), which are isolated as such or in the form of pharmaceutically acceptable salts.

Patentansprüche

1. Verbindungen, die durch die allgemeine, unten angeführte Formel (I)



(I)

dargestellt werden können und in denen:

- X CH oder N ist;
- R H, Cl oder OR_1 ist, wobei R_1 H oder eine Alkylgruppe mit ein bis drei Kohlenstoffatomen ist,
- Het die 3-Endotropylgruppe (d.h. die 8-Methyl-8-Azadicyclo[3.2.1]oct-3-yl-Gruppe) oder die 3-Quinuclidylgruppe (d.h. die 1-Azadicyclo[2.2.2]oct-3-yl-Gruppe) ist,

und deren aus pharmazeutisch zulässigen anorganischen oder organischen Säuren hergestellte Salze.

2. Verbindungen nach Anspruch 1, in denen X CH ist.

3. Verbindungen nach Anspruch 1, in denen X N ist.

4. Verbindungen nach Anspruch 2, in denen Het die 3-Endotropylgruppe ist.

5. Verbindungen nach Anspruch 2, in denen Het die 3-Quinuclidylgruppe ist.

6. Verbindungen nach Anspruch 3, in denen Het die 3-Endotropylgruppe ist.

7. Verbindungen nach Anspruch 3, in denen Het die 3-Quinuclidylgruppe ist.

8. Pharmazeutisches Präparat, das als eine aktive Substanz zumindest eine der Verbindungen nach Anspruch 1 oder ein pharmazeutisch zulässiges Salz davon enthält.

9. Pharmazeutisches Präparat nach Anspruch 8 zur therapeutischen Verwendung entsprechend seiner Wirkung bei der Behandlung von spontanem oder postoperativem Brechreiz und Erbrechen oder von Brechreiz oder Erbrechen ausgelöst durch zytostatische Therapie.

10. Pharmazeutisches Präparat nach Anspruch 8 zur Behandlung von pathologischen Zuständen des ZNS, verbunden mit Unausgewogenheiten in den physiologischen Neuronen-Konzentrationen von Serotonin, wie beispielsweise Angst, Panikattacken, Psychose, Depression, Alzheimer-Krankheit etc., oder mit anderen Ursachen, die mit dem Wirkungsmechanismus der Verbindungen nach Anspruch 1 in Wechselwirkung stehen.

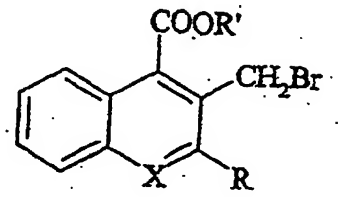
11. Pharmazeutisches Präparat nach Anspruch 8 zur Verwendung bei der Behandlung von Erkrankungen des Magen-Darm-Systems, wie nicht ulzeröser Dyspepsie, Reflux-Ösophagitis, Reizkolon und Bewegungsstörungen.

12. Pharmazeutisches Präparat nach Anspruch 8 zur symptomatischen Behandlung von Husten.

13. Pharmazeutisches Präparat nach Anspruch 8, das weiters pharmazeutisch zulässige inaktive Inhaltsstoffe enthält, ausgewählt aus der Gruppe bestehend aus Vehikeln, Bindemitteln, Aromastoffen, Aggregationshemmern, Konservierungsmitteln, Feuchthaltemitteln und Mischungen davon, oder Inhaltstoffe, welche die transdermale Absorption erleichtern oder eine kontrollierte Freisetzung der aktiven Substanz über eine Zeitspanne ermöglichen.

14. Verfahren zur Herstellung eines Derivats von der allgemeinen Formel (I), in der X und R die in Anspruch 1 festgelegten Bedeutungen haben und Het die 3-Endotropylgruppe, d.h. die 8-Methyl-8-Azadicyclo[3.2.1]oct-3-yl-Gruppe ist, das die Schritte umfasst:

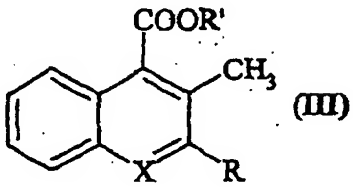
a) Reaktion von Estern der Formel (IV),



(IV)

in der X und R die oben angegebenen Bedeutungen haben und R' Methyl oder Ethyl sein kann, mit N-Bromosuccinimid in Gegenwart von Benzoylperoxid in einem organischen Lösungsmittel, wie zum Beispiel Tetrachlorkohlenstoff, bei einer Temperatur zwischen Raumtemperatur und der Rückflusstemperatur des Lösungsmittels über eine Zeitspanne zwischen einer und acht Stunden, um die entsprechenden 2-Bromomethyl-Derivate der Formel III zu erhalten;

b) Reaktion der Brom-Derivate der Formel III



(III)

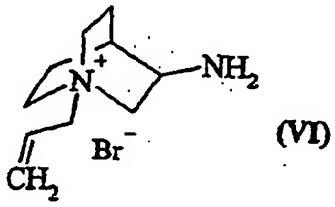
mit einer stöchiometrischen Menge eines heterozyklischen Amins der Formel (II)

NH_2-Het (II)

in der Het die 3-Endotropylgruppe ist, in Gegenwart einer inerten, tertiären Base, die als Protonakzeptor agiert, oder mit einem Überschuss des Amins (II), bei der Rückflusstemperatur eines wasserfreien Lösungsmittels, vorzugsweise Toluen, über eine Zeitspanne zwischen einer und 24 Stunden, um die entsprechenden Amidderivate der Formel (I), die als solche isoliert sind oder in Form eines pharmazeutisch zulässigen Salzes vorliegen, zu erhalten, wobei die Verbindungen der Formel (I), in der R OH ist, durch Heißsäure-Hydrolyse der entsprechenden etherischen Derivate hergestellt werden.

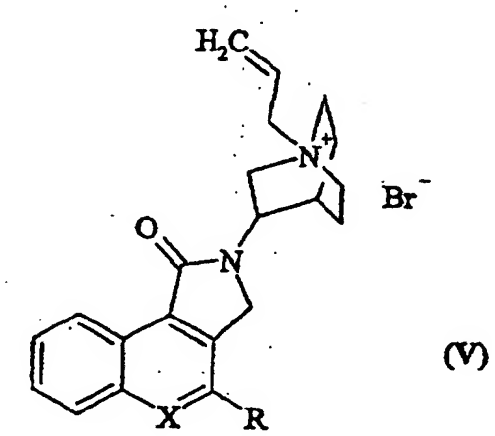
15. Verfahren zur Herstellung eines Derivats der allgemeinen Formel (I), in der X und R die in Anspruch 1 festgelegten Bedeutungen haben und Het die 3-Quinuclidylgruppe, d.h. die 1-Azadicyclo[2.2.2]oct-3-yl-Gruppe ist, das die Schritte umfasst:

Schützen des tertiären endozyklischen Stickstoffs von 3-Aminoquinuclidin durch Alkylierung mit Allylbromid, Reaktion des nicht isolierten, quaternäres Zwischenprodukt (VI)



(VI)

mit dem entsprechenden Bromderivat der Formel (III), die in Anspruch 14 angegeben ist, um das quaternäre, Ammoniumsalz der zyklischen Verbindung (V) zu erhalten,

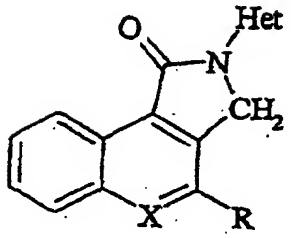


(V)

die wiederum nicht isoliert ist, und Entfernen des Schutzes bezüglich Het mit N-Dipropylamin in Dimethylformamid und in der Gegenwart einer katalytischen Menge von $Pd(PPh_3)_2Cl_2$, um die entsprechenden Amidderivate von Formel (I) zu erhalten, die als solche isoliert sind oder in Form eines pharmazeutisch zulässigen Salzes vorliegen.

Revendications

1. Composés qui peuvent être représentés par la formule générale (I) indiquée ci-dessous :



(I)

et dans laquelle

- X représente CH ou N ;
- R représente H, Cl ou OR_1 dans lesquels R_1 représente H ou un groupe alkyle ayant de 1 à 3 atomes de carbone ;
- Het représente le groupe 3-endotropyle (à savoir, le groupe 8-méthyl-8-azadicyclo[3.2.1]oct-3-yle) ou le groupe 3-quinuclidyle [à savoir, le groupe 1-azadicyclo[2.2.2]oct-3-yle], et leurs sels produits à partir d'acides inorganiques ou organiques acceptables sur le plan pharmaceutique.

2. Composés selon la revendication 1, dans lesquels X représente CH.

3. Composés selon la revendication 1, dans lesquels X représente N.

4. Composés selon la revendication 2, dans lesquels Het représente le groupe 3-endotropyle.

5. Composés selon la revendication 2, dans lesquels Het représente le groupe 3-quinuclidyle.

6. Composés selon la revendication 3, dans lesquels Het représente le groupe 3-endotropyle.

7. Composés selon la revendication 3, dans lesquels Het représente le groupe 3-quinuclidyle.

8. Préparation pharmaceutique comprenant, en tant que principe actif, au moins un des composés selon la revendication 1 ou un de ses sels acceptables sur le plan pharmaceutique.

9. Préparation pharmaceutique selon la revendication 8 en vue d'une utilisation thérapeutique conformément à son activité dans le traitement de nausée et de vomissement spontané ou post-opératoire ou de nausée ou de vomissement induit par une thérapie cytostatique.

10. Préparation pharmaceutique selon la revendication 8, pour le traitement d'états pathologiques du SNC associé aux déséquilibres dans les teneurs physiologiques en sérotonine dans les neurones, tels que, par exemple, l'anxiété, les crises aiguës d'angoisse, la psychose, la dépression, la maladie d'Alzheimer, etc., ou à d'autres causes corrélées aux mécanismes d'action des composés selon la revendication 1.

11. Préparation pharmaceutique selon la revendication 8 en vue d'une utilisation dans le traitement des troubles du système gastro-intestinal tels que la dyspepsie non ulcéreuse, l'oesophagite due au reflux, les troubles du côlon irritable et de motilité.

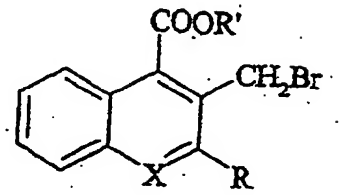
12. Préparation pharmaceutique selon la revendication 8 pour le traitement symptomatique des toux.

13. Préparation pharmaceutique selon la revendication 8, comprenant de plus des ingrédients inactifs sur le plan pharmaceutique choisis dans le groupe formé par les véhicules, les liants, les arômes, les agents de délitement, les conservateurs, les humidifiants, et leurs mélangés, ou d'ingrédients qui facilitent l'absorption transdermique ou qui permettent la libération régulée du principe actif dans le temps.

14. Procédé pour la préparation d'un dérivé de formule générale (I) dans laquelle X et R possèdent les significations données dans la revendication 1, et Het représente le groupe 3-endotropyle, à savoir, le groupe 8-méthyl-8-aza-

dicyclo[3.2.1]oct-3-yle, comprenant les étapes consistant à :

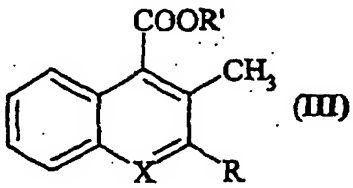
a) faire réagir des esters de formule (IV) :



(IV)

dans laquelle X et R possèdent les significations données ci-dessus et R' peut représenter le groupe méthyle ou éthyle, avec le N-bromosuccinimide en présence de peroxyde de benzoyle dans un solvant organique tel que, par exemple, le tétrachlorure de carbone, à une température comprise entre la température ambiante et la température de reflux du solvant, pendant une durée comprise entre 1 et 8 h, pour obtenir les dérivés 2-bromométhyle correspondants de formule III ;

b) faire réagir les dérivés bromés de formule III :



(III)

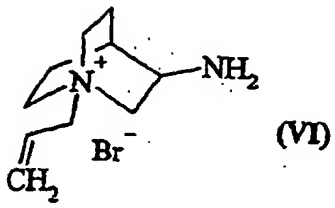
avec une quantité stoechiométrique d'une amine hétérocyclique de formule (II) :

$$NH_2\text{-Het} \qquad \text{(II)}$$

dans laquelle Het représente le groupe 3-endotropyle, en présence d'une base tertiaire inerte qui agit en tant qu'accepteur de protons, ou avec un excès de l'amine (II), à la température de reflux d'un solvant anhydre, de préférence le toluène, pendant une durée comprise entre 1 et 24 h, pour obtenir les dérivés amide correspondants de formule (I), qui sont isolés tels quels ou sous forme de sels acceptables sur le plan pharmaceutique, les composés de formule (I), dans laquelle R représente OH, étant préparés par hydrolyse acide à chaud des dérivés éther correspondants.

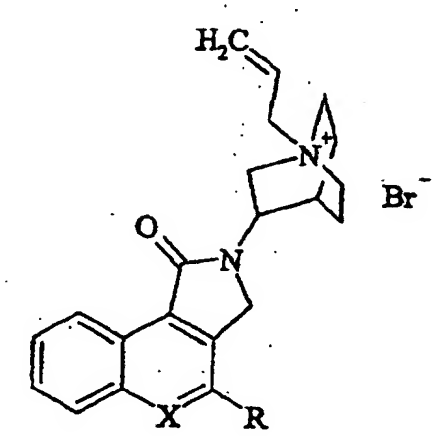
15. Procédé pour la préparation d'un dérivé de formule générale (I) dans laquelle X et R possèdent les significations données dans la revendication 1 et Het représente le groupe 3-quinuclidyle, à savoir, le groupe 1-azadicyclo[2.2.2] oct-3-yle, comprenant les étapes consistant à :

- protéger l'azote endocyclique tertiaire de la 3-aminoquinuclidine par alkylation avec le bromure d'allyle,
- faire réagir l'intermédiaire quaternisé non isolé (VI) :



(VI)

avec le dérivé bromé approprié de formule (III) indiqué dans la revendication 14, afin d'obtenir le sel d'ammonium quaternaire du composé cyclisé (V),



(V)

qui, à son tour, est non isolé, et déprotéger à chaud la n-dipropylamine dans le diméthylformamide et en présence d'une quantité catalytique de $Pd(PPh_3)_2Cl_2$ afin d'obtenir les dérivés amide correspondants de formule (I), qui sont isolés tels quels ou sous forme de sels acceptables sur le plan pharmaceutique.